Remarks

The Examiner's withdrawal of the rejection of claims 1 and 3-6 under 35 U.S.C. §112 first paragraph as not being enabled is appreciated.

Claim Objections

Claim 3 was objected to for depending on a cancelled claim. Claim 3 has been amended to depend on claim 1.

Amendments to the Claims

Claim 1 and claims dependent thereon has been amended to introduce into the claim the features relating to flexibility and not release highly acidic or inflammatory metabolites, which are inherent properties of the P4HB, but which serve to further distinguish the prior art polymers such as PLGA and P3HB which are not flexible and which in the case of PLGA release acidi or inflammatory metabolites as they degrade. Support is found in the abstract of the invention at page 4, lines 1-7.

Rejections Under 35 U.S.C. § 103

Claims 1 and 3-6 were rejected under 35 U.S.C. § 103(a) as obvious over International Application No. WO 01/54593 by Hadlock, et al. ("Hadlock) in view of Martin, et al., *Biochem. Eng. J.* 16:97-105 (2003). Claims 1 and 3-6 were also rejected as obvious over U.S. Patent No. 6,548,569 ('the 569 patent") in view of U.S. Patent No. 5,584,885 to Seckel ("Seckel") in view of evidentiary references Schlossauer, et al., Neurosurgery, 59:740-748 (2006) ("Schlossauer") and Clavijo-Alvarez, et al., *Plast. Reconstr. Surg.*, 119:1839-51 (2007) ("Clavijo").

The Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. 459 (1966). The *Graham* analysis was recently affirmed on April 30, 2007 by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

The obviousness analysis requires looking at the invention as a whole. "Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986).

Hindsight analysis, such as picking and choosing from prior art references using the claimed invention as a template, has long been forbidden. *See e.g. In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988), stating "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." In *KSR*, the Court also warned against the use of hindsight analysis in making an obviousness determination. The Court stated, "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (*KSR*, 127 S. Ct. at 1742, citing *Graham*, 383 U.S. at 36 (warning against a "temptation to read into the prior art the

teachings of the invention in issue" and instructing courts to "guard against slipping into the use of hindsight" (quoting M*onroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412, 141 U.S.P.Q. 549 (6th Cir. 1964)).

Analysis: The Claims are not obvious over Hadlock in view of Martin

The scope and content of the prior art

Hadlock

Hadlock discloses a nerve regeneration conduit which includes a porous biocompatible support which is formed into a roll (Hadlock, page 1, lines 25-28). As described on page 2, lines 1-7, the support can be a synthetic polymer - all of the ones listed on page 2 are brittle, rigid, not suitable for bending or rolling into a tube.

Martin

Martin is a review article on poly-4-hydroxybutyrate (P4HB) describing some of the progress in the development of the polymer, its properties, uses and potential applications.

Differences between the prior art and the claims

The combination of Hadlock and Martin does not recite all of the limitations of the claims.

The present invention is based on the discovery that P4HB polymers are sufficiently elastic and malleable that they can be used to make a nerve conduit. This was also shown to enhance the rate of nerve regrowth as compared to the closest prior art, which is the P3HB nerve conduit described at page 2 of the patent application.

To be obvious, the prior art would have to teach that one could have a better nerve conduit if a flexible, elastic polymer was used to form the nerve conduit. One would also have to know that P4HB had the desirable properties AND that it would somehow enhance rate of nerve regrowth.

Hadlock teaches away from the use of an elastic flexible polymer by defining polymers such as P3HB, PGA or PLGA, polycaprolacone, polyurethanes, and poly(organo)phosphazenes.

Martin teaches favorable properties for the P4HB ONCE one knows that they are desirable but the examiner has cited no art that such properties, instead of those relating to the polymers described by Hadlock, are desirable.

No art has been cited that would lead one skilled in the art to have any expectation that the rate of growth of the nerves in the nerve conduit formed of a P4HB polymer would be faster, nor why.

It is well established, and the Court in *KSR* re-affirmed, that to be obvious, one must be able to predict with a reasonable degree of certainty that the combination of the prior art will have the claimed properties. One cannot use hindsight to arrive at this conclusion.

As stated in the MPEP §2145, "the claimed combination cannot change the principle of operation of the primary reference or render the reference inoperable for its intended purpose". The Examiner's attention also is drawn to the fact that heart valves, vascular grafts, sutures and medical textile products also disclosed in Martin as employing P4HB do not contain the same pore sizes; see also Hadlock, wherein 9 different pore sizes range as desired.

The Examiner also alleged that Martin discloses that PHA polymers including poly 3-hydroxybutyrate (P3HB) and its copolymers are successful in use in peripheral nerve repair; according to the Examiner, this disclosure provides a motivation and an expectation of success in using P4HB in peripheral nerve regeneration since PHA polymers have been used to generate a nerve regeneration conduit. Martin generally states that PHA polymers, including PHO and P3HB and its copolymers with other 3-hydroxyalkanoates are showing promise in medical applications development, and specifically notes that P3HB was being evaluated for use in peripheral nerve repair. There is no disclosure or suggestion of the use of P4HB as a nerve conduit. It appears as though the Examiner is assuming that it is obvious to substitute one PHA for another i.e. the disclosure of the use of P3HB for peripheral nerve repair makes obvious selecting P4HB for use as a nerve conduit. The Examiner is wrong. There is no guidance in Martin to select P4HB with any expectation of success in making a nerve conduit. The fact that Martin states that P4HB is more stable (than poly-α-hydroxy acid materials) and useful for tissue engineering does not imply that P4HB can be used for any and every device, and one of ordinary skill in the art would not conclude as such. There are over 100 different PHA's and a disclosure that one of these (P3HB) has been used in peripheral nerve repair does not make obvious selecting P4HB from the group, simply because Martin discloses that P4HB is more stable than poly-α-hydroxy acid materials and is useful in tissue engineering; numerous PHA's share the same stability over poly-α-hydroxy acid materials and have been disclosed as useful in tissue engineering. There is no direction to select P4HB with any expectation of success. Furthermore, the Examiner's allegation that Martin discloses P4HB for use in tissue regeneration including

nerve regeneration is incorrect. Martin is clear about which tissues have been regenerated using P4HB (see Martin, page 97, under "Introduction"). Nerves are not included in the list. The Examiner also alleged that use of P4HB to substitute P3HB to make or improve the nerve conduits of Hadlock would be obvious because the results or nerve regeneration using a conduit of P3HB is known, and the results of substituting P3HB with P4HB are also expected because Hadlock teaches a nerve regeneration conduit comprising biodegradable polymers of PHA. Applicants respectfully disagree. As noted above, one of ordinary skill in the art knows that there are over 100 polymers of PHA, and not all PHA's will be suitable for making nerve guides. Some PHA's are elastomeric and would collapse on the regenerating nerve, others are too stiff and would be difficult to manipulate. So, absent some guidance, there would be no reason to select P4HB from the over 100 available PHA's. There is no evidence that any and every PHA will be suitable for nerve guides.

In summary, the prior art does not teach the selection of an elastic, flexible polymer, a P4HB polymer, instead of a brittle or rigid polymer, such as P3HB or the polymers disclosed by Hadlock. The prior art also does not teach that the selection of polymer alters the rate of regeneration, much less that the selection of a P4HB polymer can be used to enhance the rate of regeneration.

Evidence of Secondary considerations

As discussed above with respect to the double patenting rejection, the claims provide a nerve regeneration device which has a superior rate of axonal regeneration. The claimed device also meets the long felt but un met need for a nerve regeneration device that is not only safe, but

obtains axonal regeneration that is comparable to that obtained using a nerve graft (*see* the specification at least at page 3, lines 3-10).

Analysis: ***Claims 1 and 3-6 are not obvious over a combination of 'the 569 patent or the '764 patent, the '493 patent, the '247 patent and the '883 patent and Seckel.***

Claims 1 and 3-6 were also rejected as unpatentable over U.S. Patent No. 6,610,764 ('the 764 patent), U.S. Patent No. 6,838,493 ('the 493 patent), U.S. Patent No. 6,867,247 ('the 247 patent), U.S. Patent No. 7,179,883 ('the 883 patent), U.S. Published Application No. 2002/0156150 by Williams, et al., now U.S. Patent No. 6,838,493 ('the 493 patent) and U.S. Published Application No. 2002/017358 (presumably the Examiner meant U.S. Published application No. 2002/0173558 by Williams, et al (U.S. Application No. 10/136499), now U.S. Patent No. 6,867,247 ('the 247 patent) in view of Seckel and evidentiary references Schlossauer and Clavijo. Applicants respectfully traverse these rejections.

The scope and content of the prior art

The '569 patent, the '764 patent, the '493 patent, the '247 patent and the '883 patent all share the same specification, thus, discussion regarding these patents will be based on the '569 patent.

The '569 patent

The '569 patent discloses PHA compositions that can be used in both new and existing medical application devices formed of or including biocompatible polyhydroxyalkanoates that have controlled degradation rates (*see* abstract). The '569 patent discloses additives that can be used to alter the **degradation rates** of the PHA formulations, such as inorganic acids, additives

that form pores, modification of pendant groups or incorporation into the polymer backbone chemical linkages which are more susceptible to hydrolysis or enzymatic attack (from col. 10, line 6 until col. 12, line 15).

There is no disclosure of porosity for regrowth of nerves, no disclosure of chemical compositions for formation of sheets that can be rolled to form tubes or which are elastic and flexible enough to serve as nerve conduits. There is no disclosure of selecting a specific chemical composition to alter the rate of neural regeneration.

It is clear the only way this disclosure can be interpreted to make obvious the claimed subject matter is by using hindsight. This has been repeatedly refuted as appropriate, however - the references must make obvious the claimed subject matter, not applicants' own disclosure.

Seckel

Seckel discloses a regeneration chamber for promoting and controlling the growth of biological tissue. The regeneration chamber includes a chamber enclosing and defining a volume in which biological tissues are to be grown, an input port for injecting agents for promoting and controlling the growth of the biological tissues into the chamber, and an output port for pressure release and for removing agents and byproducts (col. 3, lines 55-65). The materials that can be used to make these devices are listed at col. 8, lines 12-28. These can apparently be degradable or non-degradable, polymer or non-polymer, tissue or synthetic, "cells" and apparently anything else known to mankind. It is not clear how a number of these materials could be used, but what is clear is that the biodegradable polymers that are listed are not flexible

or elastic nor do they have pores nor do they have any means of enhancing the rate of nerve regeneration.

The majority of these materials correspond to those that have been identified as having "significant shortcomings" - see page 2, lines 5-15, and reference cited therein, WO 88/06866 by Aebischer, et al., submitted with applicants' Information Disclosure Statement.

Differences between the prior art and the claims

A combination of the '569 patent and Seckel does not yield the claimed nerve regeneration device. Neither the '569 patent nor Seckel discloses a nerve regeneration device formed of a P4HB polymer, with the recited pore size range. The '569 patent discloses that the rate of degradation of the devices may be enhanced by additives which form pores and that the diameter of the pore-forming particles may suitably be between nanometers and 500 microns i.e. the range of the pore size is from greater than 0.001 microns to 500 microns. There is no disclosure to select from within this wide pore range to arrive at the narrower pore range of 5-500 microns recited in the claims or any expectation that there would be benefits associated with such a pore size selection with respect to nerve regeneration. As stated in the MPEP §2144 "if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus".

Applicants respectfully disagree with the Examiner's allegation that the '569 patent shows conduits having both a large range and a narrow range or pore sizes. The '569 patent discloses the diameter of the particles that can be used to form pores as between nanometers and

500 microns and shows an example of how to create such pores using sodium chloride crystals between 80 and 180 μm. This is not tantamount to a disclosure of a nerve regeneration device having a pore size between 80 and 180 μm, nor is there any teaching leading one skilled in the art to such a device or method of manufacture. Applicants are not claiming creating pores in a polymeric material. The '569 patent discloses a wide pore range that is relevant to enhancing polymer **degradation**; not that relates to nerve regeneration The present application discloses a combination of polymer selection and relevant pore size for the claimed device, that provides unexpected nerve regeneration (discussed below). The Examiner has provided no reason why one of ordinary skill in the art would select a pore size of between 80 and 180 μm (exemplified in the '569 patent) from the large range disclosed in the '569 patent (relevant for improved **degradation** of numerous devices) and apply this narrow range to nerve regeneration devices specifically. The '569 patent considered as a whole teaches ways to alter rates of degradation; not methods to improve rates of nerve regeneration.

With respect to the Examiner's evidentiary references (Schlossauer and Clavijo), Applicants are unclear as to how the Examiner arrived at the conclusion that these references disclose that NEUROTUBE™ has a pore size of 30-50 μm, nor its relevance to what is claimed. Clavijo discloses nerve guides made by incorporating Cultispheres within polycaprolactone (CultiGuides) and compares their CultiGuides with Neurotubes (see Clavijo, page 1840, paragraph bridging left and right columns and second paragraph right col.). Under Materials and Methods, Clavijo discloses their nerve guide fabrication, which they made porous by incorporation of sodium chloride crystals 30-50 μm in diameter. This disclosure is not about the

NEUROTUBE™, it is about the CultiGuide disclosed in Clavijo; Clavijo is not prior art to this application. Schlossauer does not mention a pore size range.

Significantly, the articles use polycaprolactone which is a very brittle polymer. Even after applicants' filing date, there was still no recognition in the field that one could use a flexible, degradation porous polymer which would be suitable for nerve regeneration **and** enhance the rate of nerve regeneration.

Evidence of Secondary considerations

Even if the examiner has made a *prima facie* case of obviousness (which is believed not to be the case, the unexpected results rebut this. This evidence shifts the burden back to the examiner to establish why the prior art makes obvious the claimed subject matter, using objective evidence, not mere argument.

As stated above, the claims are drawn to a flexible P4HB nerve regeneration device which has a superior rate of axonal regeneration when compared with the axonal generation in the prior art. The MPEP (§2144.05) states "Applicant can rebut a presumption of obviousness based on a claimed invention that falls within a prior art range by showing "(1) [t]hat the prior art taught away from the claimed invention...or (2) that there are new and unexpected results relative to the prior art." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004)".

As discussed above, the prior art teaches away from a flexible polymer to make a nerve regeneration conduit.

Moreover,'569 patent associates no effect of pore size on nerve regeneration and provides a wide pore size range that can be used to enhance degradation of the devices disclosed therein. What is relevant in the '469 patent is the percentage porosity (see Example 4), not the pore size, with devices that are 80% more porous degrading faster-thus, according to the disclosure in the '469 patent, a device with a pore size range of 0.002-0.9 microns, for example, would be expected to show enhanced degradation so long as it is 80% porous.

The Examiner has provided no reason why one of ordinary skill in the art would select (1) P4HB polymer; (2) flexible material; (3) defined pore size); from the general disclosure in the '569 patent and have any expectation of improving nerve regeneration over the levels shown in the prior art. This is not obvious from any prior art combination. Thus, at least for the reasons discussed above, claims 1 and 3-6 are non obvious over the cited art.

Rejection Under 35 U.S.C. § 112

Claims 1 and 3-6 were rejected under 35 U.S.C. §112 second paragraph as indefinite. According to the Examiner, the term "suitable" in the claims is relative, rendering the claims indefinite. Applicants respectfully disagree. One of ordinary skill in the art would understand the word suitable as used in claim 1. The word suitable means "meant or adapted for an occasion or use". One of ordinary skill in the art knows how to adapt a sheet or tube for nerve repair. Therefore, claims 1 and 3-6 are definite. However, solely to facilitate prosecution, the objected to term has been deleted from the claims.

Double Patenting Rejection

Claims 1 and 3-6 were rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-34 of U.S. Patent No. 6,610,764 to Martin, et al. ("the '764 patent"), claims 1-4 and 6-28 of U. S. Patent No. 6,838,493 to Williams, et al. ("the '493 patent"), claims 1-3 and 5-20 of U.S. Patent No. 6,548,569 to Williams, et al., ("the '569 patent"), claims 1-4 and 6-30 of U.S. Patent No. 6,867,247 to Williams, et al. ("the '247 patent"), claims 30 and 35-61 of U.S. Patent No. 7,179,883 to Williams, et al. ("the '883 patent").

Claims 1 and 3-6 were also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-18 and 21-25 of pending application No. 10/835,926 Martin, et al., ("the '926 application) and claims 1-8 of pending application No. 11/193,580 by Rizt. ("the '580 application"). Applicants respectfully traverse these rejections for the reasons set forth below.

First it should be noted that for a double patenting rejection, **only** the claims are taken into consideration; not the specification. The differences in disclosure relating to the specification are discussed above. Even if one looks at the specification as well as the claims, the claims do not make obvious the claimed subject matter for the same reasons discussed above.

The patents cited by the examiner are not all commonly owned with this application, which is assigned to Tepha. For clarification, the patents have been divided into groups based on common ownership and those which are owned by a separate entity. The equitable doctrine relating to double patenting can only be applied in the former case.

Patents Owned by Tepha

U.S.S.N 10/835,926

Inventors: Martin, David P; Rizk, Said; ; Ahuja, Ajay; ; Williams, Simon F.; *(Sherborn, MA)*

Assignee: Tepha, Inc

U.S.S.N. 11/193,580

Inventors:Rizk; Said

Assignee: Tepha, Inc

Patents Owned by Metabolix:

U.S. Patent No. 6,610,764

Inventors: Martin; David P., Skraly; Frank, Williams; Simon F.

Assignee: Metabolix, Inc.

U.S. Patent No.6,838,493

Inventors: Williams; Simon F., Martin; David P., Skraly; Frank A.

Assignee: Metabolix, Inc

U.S. Patent No.6,548,569

Inventors: Williams; Simon F., Martin; David P. , Skraly; Frank A.

Assignee: Metabolix, Inc

U.S. Patent No.6,867,247

Inventors: Williams; Simon F., Martin; David P., Skraly; Frank A.

Assignee: Metabolix, Inc.

U.S. Patent No.7,179,883

Inventors: Williams; Simon F., Martin; David P. , Skraly; Frank A.

Assignee: Metabolix, Inc

Legal Standard for Double Patenting

Double patenting results when the right to exclude granted by a first patent is unjustly extended by the grant of a later issued patent. *In re Van Ornum*, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Zickendraht*, 138 U.S.P.Q. 22 (C.C.P.A. 1963) (Rich, J., concurring). It is clear that this situation can only arise if there is common ownership. Both 37 C.F.R. and 35 U.S.C. makes clear the necessity for common ownership; the MPEP affirms this requirement.

37 C.F.R. 1.78(d) provides "Where an application claims an invention which is not patentably distinct from an invention claimed **in a commonly owned patent with the same or a different inventive entity**, a double patenting rejection will be made in the application.

When determining whether the claims of an application define an invention that is an obvious variation of an invention defined in the claims of a patent, the claims of the application are compared with the claims in the patent, **the disclosure in specification of the patent is not considered in the analysis** (*see* MPEP §§ 800-822). The MPEP explains that "[a] double patenting rejection of the obviousness-type is 'analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. § 103' except that the patent principally underlying the double patenting rejection is not considered prior art." MPEP § 804(II)(B)(1), citing *In re Braithwaite*, 379 F.2d 594, 154 U.S.P.Q. 29 (CCPA 1967). Therefore, analysis employed in an obviousness-type double patenting rejection parallels the guidelines for a 35 U.S.C. § 103

obviousness determination but only with respect to the claims, not in view of the specification. *Id.*, citing *In re Braat*, 937 F.2d 589, 19 U.S.P.Q.2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985).

Analysis

The'764, the '493, the '569, the '247 and the '883 patents

It clear that this rejection is legally improper with respect to the '764 patent, the '493 patent, the '569 patent, the '247 patent and the '883 patent. Thus the claims should only be rejected under 35 U.S.C. §102 and/or §103, discussed below. The patents listed above are owned by Metabolix, Inc. The pending application is owned by Tepha, Inc. Thus there is no common ownership between the cited patents and the present application. The claims in the present application should only be rejected under §102 and/or §103 over the Metabolix patents. Even if such a rejection were made, the claims cited by the Examiner do not anticipate or make obvious the present claims.

Anticipation

None of the claims cited by the Examiner define the claimed nerve regeneration device (admitted by the Examiner on page 4, last paragraph in the Office action mailed 10/23/07).

Therefore, none of the claims anticipate claims 1 and 3-6 of the present application.

Obviousness

The Scope and Content of the Cited claims

Claims 1-34 of the '764 patent

Claims 1-11, 26-32 and 34 define a biocompatible polyhydroxyalkanoate composition that has a controlled degradation rate of less than one year by hydrolysis *in vivo*, selected from the group consisting of polyhydroxyalkanoate compositions wherein monomeric units are incorporated as chemical linkages into the polymer backbone which alter the chemical stability of the polymer, wherein linkages are incorporated into the polymer backbone which alter the chemical stability of the polymer, and wherein pendant groups are incorporated into the polymer which alter the chemical stability of the polymer, wherein the polyhydroxyalkanoate has a weight-average molecular weight in the range between 10,000 to 10,000,000 Dalton.

Claims 12, 25, 33 and 34 recite all of the limitations of claim 1 and additionally require that the claimed composition contain more than two functional groups selected from the group consisting of reactive groups which can cleave the polymer backbone by an intramolecular or intermolecular reaction, acidic or basic groups, and units that modulate the reactivity of the ester linkage selected from the group consisting of 2-hydroxyacids, 2-hydroxyethoxy acetic acid, 2-hydroxypropoxy acetic acid, amino acids, amino alcohols, and diacids, which are positioned within the polymer backbone to increase the rate of degradation, triols, and tetraols.

These claims do not relate to nerve regeneration devices; do not lead one to make a flexible porous nerve regeneration device; do not teach one of ordinary skill in the art that

porosity or polymer composition would have any impact on nerve regeneration, and therefore do not make obvious the claims of this application.

Claims 1-4 and 6-28 of the '493 patent

Claims 1-4 and 6-28 of the '493 patent define a device comprising a biodegradable polyhydroxyalkanoate polymer composition that has a controlled degradation rate, under physiological conditions, wherein the average molecular mass loss of the polymer decreases 20% to 50% over a ten week time period in vivo or wherein the percent mass loss is greater than 5% over a six week period in vivo, wherein the degradation rate of the polyhydroxyalkanoate polymer is manipulated through addition of components to the polymeric composition, selection of the chemical composition, molecular weight, processing conditions, or form of the composition, wherein the polyhydroxyalkanoate polymer has a weight average molecular weight of between 10,000 and 10,000,000 Daltons, and wherein the device is selected from the group consisting of sutures, suture fasteners, meniscus repair devices, rivets, tacks, staples, screws, bone plates and bone plating systems, surgical mesh, repair patches, slings, cardiovascular patches, orthopedic pins, adhesion barriers, stents, guided tissue repair/regeneration devices, articular cartilage repair devices, nerve guides, tendon repair devices, atrial septal defect repair devices, pericardial patches, bulking and filling agents, vein valves, bone marrow scaffolds, meniscus regeneration devices, ligament and tendon grafts, ocular cell implants, spinal fusion cages, skin substitutes, dural substitutes, bone graft substitutes, bone dowels, wound dressings, and hemostats.

The claims in this patent relate to rate of degradation; not nerve regeneration devices that have an enhanced rate of regeneration. One skilled in the art would be more likely to look at polymers having a particular rate of degradation and not at the rate of nerve regeneration.

Claims 1-3 and 5-20 of the '569 patent

The claims define a biodegradable polyhydroxyalkanoate composition comprising a polyhydroxyalkanoate polymer having a controlled degradation rate of less than one year in vivo, under physiological conditions, wherein the degradation rate of the polyhydroxyalkanoate polymer is manipulated through addition of components to the polymeric composition, selection of the chemical composition of the polyhydroxyalkanoate polymer through selection of monomeric units, as chemical linkages, which are incorporated into the polymer, by alteration of the linkages, chemical backbone or pendant groups, molecular weight, processing conditions, or form of the composition, and wherein the polyhydroxyalkanoate polymer has a weight average molecular weight of between 10,000 and 10,000,000 Dalton; and wherein the form of the composition refers to the porosity and surface area of the composition.

The same comments apply to this patent as to the previous two. The disclosure relates to the advantages of PHAs in general, and specifically as to rate of degradation as a function of molecular weight and/or porosity.

Claims 1-4 and 6-30 of the '247 patent

The claims define a method of enhancing the healing of a wound, injury, or defect in a site in a patient, comprising administering at the site a device comprising a biocompatible polyhydroxyalkanoate composition wherein the degradation rates of the polyhydroxyalkanoates

is manipulated through addition of components to the polymeric composition, selection of the chemical composition, molecular weight, processing conditions, or form of the composition, wherein the mass loss of the polyhydroxyalkanoate, as measured by gas chromatography, is greater than 5% over a six week period *in vivo*, or wherein the average molecular mass of the polyhydroxyalkanoate, as measured by gel permeation chromatography, decreases 20% to 50% over a ten week period *in vivo*, and wherein the device is selected from the group consisting of sutures, suture fasteners, meniscus repair devices, rivets, tacks, staples, screws, bone plates and bone plating systems, surgical mesh, repair patches, slings, cardiovascular patches, orthopedic pins, adhesion barriers, stents, guided tissue repair/regeneration devices, articular cartilage repair devices, nerve guides, tendon repair devices, atrial septal defect repair devices, pericardial patches, bulking and filling agents, ligament and tendon grafts, ocular cell implants, spinal fusion cages, heart valves, vascular grafts, skin substitutes, dural substitutes, bone graft substitutes, bone dowels, wound dressings, and hemostats.

The claims in this patent also focus on PHAs having controlled degradation rates, not flexibility and porosity for a nerve regeneration device which provides an enhanced rate of degradation.

Claims 30 and 36-61 of the '883 patent

Applicants are unclear as to which claims the Examiner is referring to, since the '883 patent does not have claims 36-61. Thus, Applicants will discuss all of the claims in the '883 patent.

Claims 1 and 5-30 define a device comprising a biodegradable polyhydroxyalkanoate polymer composition that has a controlled degradation rate of less than one year, under physiological conditions, wherein the degradation rate of the composition is manipulated through addition of components to the polymeric composition, selection of the chemical composition, molecular weight, processing conditions, or form of the composition, wherein the device is selected from the group consisting of rotator cuff repair devices, temporary wound support devices, bladder patches, pledgets, soft tissue reinforcement devices, vascular patches, devices for artrial wall repair, bone marrow scaffolds, ligament repair devices, rods, washers, screws, pins, struts, plates, and staples used in spinal fusion cages, stents, sewing rings, stiffners used in heart valve supports, cell encapsulation devices, coated devices, defect filling devices, organ patches, organ salvage devices, staple line reinforcement devices, pelvic floor reconstruction devices, devices for closure of ventricular septal defects, drug delivery devices, devices for delivery of biological factors, and devices comprising encapsulated proteins, antibodies, enzymes, peptides, polysaccharides, saccharides, organic drugs, inorganic drugs, nucleic acids, antigens, inhibitors, clot dissolving agents, hormones, nucleic acid, and/or lipids.

Claims 2-4 define a method of making the device defined by claim 1.

The differences between claims cited by the Examiner and claims 1 and 3-6 of the present application.

None of the claims cited by the Examiner define a nerve regeneration device in the form of a porous conduit with pores having a diameter of between 5 and 500 microns as recited in claims 1 and 3-6 of the present application.

Moreover, there is nothing in any of the claims that would lead one of ordinary skill in the art to select the pore sizes recited in the claims.

The Examiner admitted that the prior art claims do not specify a conduit as claimed, with pore size between 5-500 microns. However, according to the Examiner, the specification teaches a process of generation of a conduit with a pore size between nanometers-500 μm. Applicants respectfully draw the Examiner's attention to the fact that the claims, not the specification should be analyzed (*see* MPEP §§ 800-822); as admitted by the Examiner, the claims do not specify a conduit with the claimed pore sizes. Furthermore, there is nothing in any of the claims cited by the that would direct one of ordinary skill in the art to modify the claims to arrive at the recited pore sizes.

Evidence of Secondary considerations

Secondary considerations to be considered include commercial success, long felt but unresolved needs, failure of others, unexpected results, etc.

Various materials such as silicone rubber, polyglactin mesh, acrylic copolymer tubes and other polyesters have been tested as candidates for nerve channel conduits. These however have been reported to include several significant shortcomings (*see* the present specification at least at page 2, lines 5-10). Several researches have investigated the use of poly-3-hydroxybutyrate (P3HB) in a bid to improve upon these results with positive results. However the rate of nerve regeneration obtained with P3HB is inferior when compared to the results obtained with a nerve graft. By combining the polymer and pore size range selection recited in claim 1, the present claims provide a nerve regeneration device with which unexpected nerve regeneration

(1mm/day) is obtained when compared to 0.3mm/day (i.e.10mm/30day) for example, using P3HB (*see* Hazari, et al. *Br. J. Hand Surg.*, 653-57 (1999) (Submitted with the Information Disclosure Statement filed on August 30, 2006 and considered by the Examiner on February 2, 2007). Thus, the claims provide a nerve regeneration device which has a superior rate of axonal regeneration. The claimed device also meets the long felt but unmet need for a nerve regeneration device which obtains axonal regeneration that is comparable to that obtained using a nerve graft (*see* the present specification at least at page 3, lines 3-10).

For at least the reasons set forth above, claims 1 and 3-6 of the present application are nonobvious over the cited claims.

The '926 and the '580 applications

The '926 and the '580 applications are commonly owned with the present application; thus a double patenting rejection is legally proper. However, Applicants respectfully traverse this rejection because the claims in the '926 and the '580 applications are not obvious variants of the present claims.

Scope and Content of the Cited Claims

The '926 Application

Claims 1-11 define a fiber comprising poly-4-hydroxybutyrate polymer wherein the fiber has a tensile strength of greater than 126 MPa.

Claims 12-18 define a device comprising one or more fibers comprising poly-4-hydroxybutyrate polymer having a tensile strength of greater than 126 MPa selected from the group consisting of a medical textile, tube, general surgical mesh, hernia mesh, pericardial patch,

anti-adhesion patch, cardiovascular patch, guided tissue regeneration patch, sling, monofilament suture, multifilament suture, braid, ligament, tendon, meniscus repair device, cartilage repair device, nerve guide, stent, vascular graft, and dura.

Claims 21-25 define a device selected from the group consisting of a medical textile, tube, general surgical mesh, hernia mesh, pericardial patch, anti-adhesion patch, cardiovascular patch, guided tissue regeneration patch, sling, monofilament suture, multifilament suture, braid, ligament, tendon, meniscus repair device, cartilage repair device, nerve guide, stent, vascular graft, and dura, the device comprising one or more fibers comprising poly-4-hydroxybutyrate polymer wherein the fiber has a tensile strength of greater than 126 MPa.

The '580 Application

Claims 1-8 of the '580 application define a polymeric filament comprising 4-hydroxybutyrate or copolymers thereof, wherein the filament has an elongation to break from 17% to 85%, a Young's modulus of less than 350,000 psi, or a load at break between 1100 and 4200 g, and is produced by extrusion, orientation, relaxation and annealing of the extruded filament.

Differences between the cited claims and Claims 1 and 3-6 of the present application

None of the claims cited by the Examiner recite any of the claim limitations. The Examiner has provided no reason why one of ordinary skill in the art would arrive at the claimed conduit from claims 1-8 of the '580 application or claims 1-18 and 21-25 of the '926 application. There is nothing in any of the cited claims that would lead one of ordinary skill in the art to

select the pore sizes recited in claim 1 of the present application for a nerve regeneration device.

Although the Examiner acknowledged that none of the cited claims define the claimed device, the Examiner's reasons for the rejection are that the specification of these applications is similar to the specification of the '569 patent, which discloses how to make a device with a pore size between nanometers to 500 micron. This is not the correct legal analysis, as discussed above, the specification should not be used to support a double patenting rejection, the analysis should be on the claims. Furthermore, even if the specification were applicable, there is no mention of pore sizes in the specification of the cited applications.

For at least the reasons discussed above, Applicants submit that claims 1 and 3-6 of the present application are not non obvious over the cited claims.

Allowance of claims 1 and 3-6 is respectfully solicited.

Respectfully submitted,

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